Proposed Decision Memo for Clinical Trial Policy (CAG-00071R2)

Decision Summary

This memorandum announces the proposed determination of the Centers for Medicare & Medicaid Services (CMS) on whether items and services delivered as part of a clinical research study are reasonable and necessary. We propose the followingrevisions to the current Medicare Clinical Trial Policy (CTP), which we will rename as the Clinical Research Policy (CRP) in order to make clear the full scope of the policy.

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Proposed Decision Memo

TO: Administrative File: CAG-00071R2
Clinical Research Policy

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DATE: July 19, 2007

SUBJECT: Proposed Decision Memorandum for Second Reconsideration of the Clinical Trial Policy, Renamed the Clinical Research Policy (CAG -00071R2)

I. Proposed Decision Summary

This memorandum announces the proposed determination of the Centers for Medicare & Medicaid Services (CMS) on whether items and services delivered as part of a clinical research study are reasonable and necessary. We propose the followingrevisions to the current Medicare Clinical Trial Policy (CTP), which we will rename as the Clinical Research Policy (CRP) in order to make clear the full scope of the policy.

1. Setting forth the scope of the policy by defining “clinical research” and renaming the overall NCD to clearly include all clinical research.

2. Replacing the requirements and other necessary characteristics for qualifying clinical trials under the Clinical Trial Policy with scientific and technical standards for certified clinical research studies.

3. Preserving CMS authority to permit Coverage with Evidence Development (CED) when appropriate.

4. Redefining coverage for qualifying clinical research studies or CED to avoid confusion with terms used in other contexts, using the term “usual patient care.”

5. Defining “routine clinical services” that are included in “usual patient care.”

6. Clarifying the extent to which “investigational clinical services” are included in “usual patient care.”

7. Clarifying that coverage does not include “administrative services” required to carry out studies but not required to furnish usual patient care.

8.

Establishing a process that clinical research study sponsors/principal investigators must use to certify to CMS that their study meets the standards described in this policy.

9.

Enumerating types of clinical research studies that are excluded from this policy.

10.

Clarifying the relationship between coverage under this policy and local coverage determinations (LCDs).

These proposed changes are described in more detail below. The proposed NCD language is in the Appendix.

This second reconsideration proposed determination builds upon the input from the previous reconsideration. We are requesting public comments on this proposed determination pursuant to Section 731 of the Medicare Modernization Act. After considering the public comments, we will make a final determination and issue a final decision memorandum.

II. Background

On September 19, 2000, the Health Care Financing Administration (now CMS) implemented a CTP through the NCD process. The CTP was developed in response to a June 7, 2000 Executive Memorandum. The NCD was set forth in the NCD Manual at section 310.1 (the 2000 NCD).

That 2000 NCD limited the payment for items and services provided to Medicare beneficiaries in qualified trials to routine costs. In general, the policy defined “routine costs” as those items and services that would generally be covered for Medicare beneficiaries outside a trial. As noted by commenters on the April 10, 2007 proposed decision memorandum, this definition contained language that was read as ambiguous with respect to the items or services that were the subject of the investigation.

In July 2006, CMS began a reconsideration of the 2000 NCD. CMS convened a Medicare Evidence Development & Coverage Advisory Committee (MedCAC) to obtain public input and provide recommendations to CMS; asked AHRQ to provide recommended changes, and received public comments on the proposed decision. After the publication of our proposed decision memorandum on April 10, 2007, we received several comments from hospitals and others suggesting that Medicare contractors had been paying claims involving patients in various types of clinical research outside the terms of the clinical trial policy. These claims may not have always been identified as clinical trial items or services. The commenters sought an assurance that funding will continue for the usual patient care associated with research in a hospital.

In addition, commenters identified additional Medicare policies and statements that are not identical to the coverage provided under the 2000 NCD, and the existence of these policies may have been confusing or ambiguous. As a result, in the initial reconsideration, CMS adopted only the following two proposed changes:

1. The addition of Coverage with Evidence Development (CED).
2. Clarification that the item under investigation was considered a routine cost if covered outside the trial.

III. Authority

In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, must not be otherwise excluded from coverage, and must be reasonable and necessary as defined in section 1862(a)(1)(A). Section 1862(a)(1)(A) is an exclusion of items and services that do not meet the reasonable and necessary standard which states:

Notwithstanding any other provision of this title, no payment may be made under part A or part B for any expenses incurred for items or services—which, except for items and services described in a succeeding subparagraph, are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member…

A succeeding subparagraph, section 1862(a)(1)(E), provides additional authority for coverage of items and services under certain federally funded or supported clinical research. This section states:

In the case of research conducted pursuant to section 1142, which is not reasonable and necessary to carry out the purposes of that section.

Generally, when making a national coverage determination, CMS evaluates whether or not items or services falling within Medicare benefit categories are reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. We customarily review specific evidence to determine whether the item or service is reasonable and necessary in the specific intervention at issue and, as part of that review, whether the intervention will improve health outcomes for Medicare patients.

Evidence-based review is not feasible for the broad range of items or services that can be furnished to patients enrolled in a clinical research trial. As discussed below, CMS therefore relies on the integrity of the clinical research protocol in lieu of our usual evidence-based review. In this policy we extend Medicare coverage only to clinical research that is likely to result in evidence that we would accept to demonstrate that the specific interventions are reasonable and necessary, and that contain protections to maximize the improvement of health outcomes for Medicare patients. To that end, this policy includes standards for clinical research that are a condition of Medicare coverage.

IV. Discussion

During the two 30-day public comment periods of the initial reconsideration when CMS was first reconsidering the CTP, the Agency received public comments from 90 different groups and individuals. The comments originated from academic health centers, specialty research groups, the medical device and pharmaceutical industry, professional societies, advocacy and interest groups, and lawyers.

We discuss below the comments received during the initial reconsideration that led to this second reconsideration and the significant changes that are proposed in this second reconsideration. We will fully address all comments in our final decision memorandum.

A. GENERAL ISSUES

CMS received many comments stating that it appeared that the April 10, 2007 proposed decision would limit privately funded trials that were being paid prior to the announcement of that policy. This concern was based on an interpretation that the 2000 Clinical Trial Policy established a second path to Medicare coverage of items and services within Federally funded trials, but did not restrict or otherwise affect Medicare coverage under privately funded trials.

Because of this apparent confusion concerning the applicability of the 2000 NCD, we are proposing to set forth the scope of the policy by defining “clinical research” and renaming the overall NCD to include all clinical research. We are further proposing to replace the requirements for qualifying clinical trials with new standards that ensure that coverage for Medicare beneficiaries participating in research studies is consistent across all types of studies, including Federally funded and privately funded trials. We are also proposing to define the items or services that would be covered in qualifying clinical research to maintain consistency across the Medicare program (and making clear that coverage does not include administrative costs of the clinical research). We have reviewed the Medicare regulations, manual instructions, and other policy statements to ensure that this definition will be consistent with other Medicare policies. CMS is considering rulemaking to resolve these issues.

In addition to ensuring consistency of wording, we are proposing a process that will allow study sponsors/principal investigators to certify to CMS that their study meets the standards described in this policy. This modification will ensure that all qualifying clinical research studies, whether publicly funded or privately funded, will be eligible for coverage under the final NCD. More details of the proposed changes are discussed below.

B. SCOPE OF CLINICAL RESEARCH POLICY DEFINITION OF CLINICAL RESEARCH

Comments on the initial reconsideration indicated that the 2000 CTP was not clear in setting forth its overall scope; in particular, there was uncertainty as to whether its scope was limited to federal funded clinical trials. To clarify the scope of the policy, we propose to rename the policy as the Clinical Research Policy, and we propose to define clinical research. We had numerous requests for a definition during the previous reconsideration. We are proposing the following:

Clinical research, for purposes of this NCD, means any systematic investigation involving human participants which is designed to contribute to generalizable knowledge and which involves a clinical intervention, care delivery strategy, or diagnostic technique designed to potentially improve predefined health outcomes.

Some examples of the types of clinical research studies that might be supported follow, but this list should not be considered exhaustive:

- Randomized controlled trials and other comparative clinical studies of effectiveness and comparative effectiveness;
- Observational clinical studies of outcomes of specific interventions, primary and secondary prevention strategies, or of implemented strategies related to delivery of care or testing of hypotheses regarding health services research; and
- Clinical studies of diagnostic tests, including measurements of sensitivity and specificity, and impact on physician decision making and patient outcomes.

C. STANDARDS FOR CLINICAL RESEARCH TO SUPPORT MEDICARE COVERAGE OF ITEMS AND SERVICES

The purpose of technical and scientific standards is twofold; 1) to ensure that all sponsors and investigators conduct clinical research so that Medicare covered items and services are reasonable and necessary to obtain valid research outcomes and for treating research participants, and 2) to maximize the health outcomes (and minimize risk) for Medicare beneficiaries.

All bona fide disciplines that conduct research have standards that describe good research practices whether the research is in the field of management, health care, clinical trials, or marketing. It is imperative that all researchers adhere to the highest standards of integrity. In order for researchers to adhere to high standards, the standards must be credible and designed to apply to all research within the specific discipline. The rule at 42 CFR § 52(h) describes the scientific peer review of research grant applications and research and development contract projects for The National Institutes of Health.[1] In addition, 42 CFR § 52(h)(8) provides the specific criteria by which the peer review members must assess the study protocol for its overall impact on the research subject. Eight matters are specifically addressed as shown below:

(a) The significance of the goals of the proposed research, from a scientific or technical standpoint;

(b) The adequacy of the approach and methodology proposed to carry out the research;

(c) The innovativeness and originality of the proposed research;

(d) The qualifications and experience of the principal investigator and proposed staff;

(e) The scientific environment and reasonable availability of resources necessary to the research;

(f) The adequacy of plans to include both genders, minorities, children and special populations as appropriate for the scientific goals of the research;

(g) The reasonableness of the proposed budget and duration in relation to the proposed research; and

(h) The adequacy of the proposed protection for humans, animals, and the environment, to the extent they may be adversely affected by the project proposed in the application.

As with other federal agencies, CMS believes minimum standards for Medicare supported clinical research are needed to ensure that items and services furnished to Medicare beneficiaries in clinical research are reasonable and necessary, and for the protection of participants who volunteer to participate in studies, in this case Medicare beneficiaries. Any study that removes the ability of physicians and patients to make choices as to their healthcare exposes that patient to increased risks. In addition, there are numerous studies that are of little benefit to patients or to the Medicare program.

Furthermore, CMS believes, in concert with other federal agencies, that appropriate study design is critical to ensure that not only are participants in research studies exposed to the least risk possible, but also to ensure that the results from the study will be useful in improving healthcare delivery. Poorly designed studies will likely produce results of little benefit in improving outcomes.

Thus, CMS is proposing to set forth scientific and technical standards for clinical research to be applied to clinical research in which providers, practitioners, or suppliers are requesting payment for usual patient care provided to Medicare beneficiaries participating in the study.

These standards were crafted purposely to update the 2000 CTP with input from other Federal Agencies that conduct health research, the MedCAC, and AHRQ. We are proposing that they be established as standards of a clinical research study in this revised Clinical Research Policy:

- The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
- The research study is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
- The research study does not unjustifiably duplicate existing studies.
- The research study design is appropriate to answer the research question being asked in the study.
- The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
- The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46. If a study is FDA-regulated, it also must be in compliance with 21 CFR Parts 50 and 56.
- All aspects of the research study are conducted according to the appropriate standards of scientific integrity.
- The research study has a written protocol that clearly addresses, or incorporates by reference, the Medicare standards.

- The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Studies of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life-threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.
- The clinical research study is registered on the ClinicalTrials.gov website by the study sponsor/principal investigator prior to the enrollment of the first study subject.
- The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. However, a full report of the outcomes must be made public no later than three (3) years after the end of data collection.
- The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
- The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

D. EXCLUSIONS FROM CLINICAL RESEARCH STANDARDS FOR MEDICARE COVERAGE OF ITEMS AND SERVICE.

During the initial reconsideration that resulted in the policy issued on July 9, 2007, commenters suggested that certain research studies that do not influence physician or patient behavior do not increase the risk to patients and, as such, should not be required to meet the clinical research standards outlined in the proposed CRP. We agree. Therefore, we propose the following language:

A number of data collection processes, while meeting the broad definition of a clinical research study, are based upon previously collected data, or data collected in such a manner as to not influence current patient management or health outcomes. The clinical items and services that are provided as the basis for these data collection processes may be determined to be reasonable and necessary under §1862(a)(1)(A).

These include:

- Simple non-comparative case reports and case series;
- Retrospective studies that evaluate events that have already occurred including studies that rely exclusively on previously collected administrative records, medical data or other available data;
- Quality assessment, quality improvement, or performance improvement studies; and

- Prospective studies in which natural human behavior is observed in a way that does not intentionally or unintentionally change or potentially change the behavior of patients, physicians and other clinical staff, control subjects, healthy volunteers, or caretakers; in which there is no assigned or pre-specified intervention that intentionally or unintentionally changes or potentially changes the behavior of patients, physicians and other clinical staff, control subjects, healthy volunteers, or caretakers; and in which there is no assigned or pre-specified intervention that changes or potentially changes medical care, medical decision-making or any medical treatments.

These studies are not required to meet the standards or approval processes outlined in this policy. All human subject protections and patient privacy rules continue to apply.

E. COVERED ITEMS AND SERVICES

The CTP provided for coverage of “routine costs” under a clinical trial, and contained certain specific included categories of covered items or services. The July 9, 2007 NCD amended the 2000 CTP to clarify that investigational items and services that would be covered outside a clinical trial would also be covered as routine costs, and also added coverage for items and services in clinical research trials for which there is some evidence of significant medical benefit, but for which there is insufficient evidence to support a “reasonable and necessary” determination (CED). The July 9, 2007 NCD provided that CED is determined through the NCD process, and is conditional on meeting standards for clinical research that ensures patient protection and the development of evidence to evaluate coverage.

In the initial reconsideration that led to the policy announced on July 9, 2007, we received numerous comments and recommendations to expand coverage to the item under investigation if it was covered outside the study. We had proposed in that reconsideration to define two (2) types of services that were eligible for coverage: routine clinical services and investigational clinical services. We learned from public comments that there was some confusion about the meaning of the term “routine care” and the proposed terms, in light of other definitions of those and similar terms in Medicare regulations and manuals.

To prevent confusion and provide consistency, we are proposing to adopt the term “usual patient care” in this NCD to define those items and services that are covered by Medicare in clinical research studies. The definition of usual patient care will include both routine and investigational clinical services.

Thus, CMS is proposing the following definitions:

Administrative services: Administrative services are defined as all non-clinical services, such as investigator or coordinator salaries; protocol development; recruiting participants; data quality assurance activities; statistical analyses; dissemination of findings; and study management. Administrative services also include clinical services provided to solely satisfy data collection and analysis needs that are not used in the direct clinical management of the patient.

Investigational clinical services: Investigational clinical services are defined as those items and services that are being investigated as an objective within the study. Investigational clinical services may include items or services that are approved, unapproved, or otherwise covered (or not covered) under Medicare.

Routine clinical services: Routine clinical services include items and services that:

- are covered for Medicare beneficiaries outside of the clinical research study;
- are used for the direct patient management within the study; and,
- do not meet the definition of investigational clinical services.

For example, routine clinical services include:

- items or services required solely for the provision of the investigational clinical services (e.g., administration of a chemotherapeutic agent);
- clinically appropriate monitoring, whether or not required by the investigational clinical service (e.g., blood tests to measure tumor markers); and
- items or services required for the prevention, diagnosis, or treatment of research related adverse events (e.g., blood levels of various parameters to measure kidney function).

Usual Patient Care: Usual patient care includes routine clinical services and investigational clinical services in clinical research when the investigational clinical services would be covered outside of the clinical research and the clinical research meets the standards for a clinical research study outlined in this policy.

In addition, we are proposing the following coverage determination:

Medicare covers usual patient care in qualified clinical research. Medicare does not cover usual patient care when such care is provided free to the Medicare beneficiary or when the study sponsor agreement with investigator sites or the informed consent documents provided to the patient specify that the care will be provided free to participants (§1862(a)(2); 42 CFR 411.4).

This proposal does not change any coverage requirement that has been developed through regulation, NCD or CMS manual instructions. Any restrictions that are applied to patient care through an NCD or local policies (including LCDs or claim adjudication) must be followed within a clinical research study unless modified through an NCD that provides CED. For more information on LCDs, see Section G below.

F. APPROVAL PROCESS

The 2000 CTP outlined two processes for ensuring that research studies enrolling Medicare beneficiaries met the standards of that policy: deeming and self-certification. Deeming allowed other Federal agencies to deem that the standards had been met through their funding and review process. Self-certification, in which trial sponsors could certify that the standards had been met, was never implemented.

During the last reconsideration of this policy, it became apparent that significant confusion existed about the deeming process and whether non-Federally funded trials were exempt from this process.

As an alternative to deeming or self-certification, many commenters recommended that Institutional Review Board (IRB) review is sufficient and that no approval process is necessary. The members of the MedCAC spent a considerable amount of time at the December 13, 2006 meeting discussing whether IRBs are appropriate mechanisms to approve clinical research studies for coverage by the Medicare program and recommended that IRB review is not sufficient to meet the goals of this policy. IRB review and CMS standards are aimed at different objectives. CMS standards are aimed to ensure that the research will generate evidence that can be used for determining Medicare coverage while IRB review is focused on informed consent and patient protection. IRBs have also expressed concern that they are underfunded to do scientific reviews of protocols, or assure that trials are registered at ClinicalTrials.gov. Thus, we do not believe it is appropriate for CMS to consider burdening IRBs to perform a more rigorous and time-consuming review that is beyond their primary purpose.

We received many comments during the initial reconsideration urging the Agency to implement the self-certification process outlined in the 2000 policy. We believe that until we clarify policy issues around coverage of usual patient care in clinical research studies through rulemaking, a self-certification process that allows study sponsors/principal investigators to certify that their study meets these standards will add appropriate protection for our Medicare beneficiaries.

Therefore, we are proposing the following:

CMS will cover usual patient care for beneficiaries enrolled in clinical research studies in which the study sponsor/principal investigator has certified to CMS that the standards in this policy have been met. CMS will notify beneficiaries, providers, and practitioners of those research studies that have certified compliance with this policy by posting the research study title and ClinicalTrials.gov registry number on our website and in the Federal Register. The ClinicalTrials.gov registry will also annotate this in its registry. Providers and practitioners will add appropriate information to their claims forms indicating that usual patient care provided to beneficiaries in research studies occurred in research studies that were listed on these sites as meeting the standards of the CRP.

Study sponsors/principal investigators wishing to have their research study listed as certified on our website, in the Federal Register and on ClinicalTrials.gov may send a letter to CMS describing the scope and nature of the clinical research, discussing each of the standards in this policy, and certifying that all standards in this policy have been met. CMS will only review this letter for completeness. Following approval of a Paperwork Reduction Act form, it will be provided on the CMS website to facilitate this submission. To be added to the list of certified studies, the letter should include the following information:

- Name of the research study
- ClinicalTrials.gov registry number ("NCT" followed by eight numbers)
- Study start date
- A point of contact with telephone number for questions if the letter is not complete.
- Discussion as to how the study meets each of the standards in this policy.

Letters should be submitted to:

Centers for Medicare & Medicaid Services
Office of Clinical Standards & Quality
Director, Coverage & Analysis Group
ATTN: Clinical Study Certification
Mailstop: C1-09-26
7500 Security Blvd
Baltimore, MD 21244

Additionally, CMS determined in the initial reconsideration that, through the national coverage determination (NCD) process, CMS may determine, through an individualized assessment of benefits, risks, and research potential, that certain items and services for which there is some evidence of significant medical benefit, but for which there is insufficient evidence to support an evidence-based determination, are reasonable and necessary only when provided in a clinical trial that meets the requirements defined in that NCD. This implemented the CED concept outlined in a previously published guidance document.[2] We will maintain this policy in this proposed decision.

G. LOCAL COVERAGE DETERMINATIONS

The 2000 CTP stated that local coverage determinations (LCDs) were not affected by the CTP. The language used resulted in confusion. Therefore, we are proposing that the CRP explain that items and services provided within clinical research studies are subject to local policies including LCDs and claim adjudication. We propose the following language:

Items and services provided within clinical research studies are subject to local policies including LCDs and claim adjudication. For information about LCDs, refer to http://www.cms.hhs.gov/DeterminationProcess/04_LCDs.asp#TopOfPage, a searchable database of Medicare contractors' local policies.

H. INVESTIGATIONAL DEVICE EXEMPTION (IDE)

The rule at 42 CFR Part 405 Subpart B specifically outlines the coverage criteria applicable to medical devices that have been provided an IDE by the FDA. This policy does not alter those criteria.

I. TRANSITION

This policy will not apply to any clinical research study that was covered under any previous policy that has begun enrollment prior to the effective date of this decision.

J. HUMANITARIAN DEVICE EXEMPTIONS

Since humanitarian use devices (HUDs) with an FDA approved humanitarian device exemption (HDE) are not addressed in this policy, local contractors may continue to make determinations about the coverage of HUDs.

V. Summary of Changes

In summary, CMS is proposing the following revisions to the current Medicare Clinical Trial Policy.

1) Setting forth the scope of the policy by defining “clinical research” and renaming the overall NCD to clearly include all clinical research.

2) Replacing the requirements and other necessary characteristics for qualifying clinical trials under the Clinical Trial Policy with scientific and technical standards for certified clinical research studies.

3) Preserving CMS authority to permit Coverage with Evidence Development (CED) when appropriate.

4) Redefining coverage for qualifying clinical research studies or CED to avoid confusion with terms used in other contexts, using the term “usual patient care.”

5) Defining “routine clinical services” that are included in “usual patient care.”

6) Clarifying the extent to which “investigational clinical services” are included in “usual patient care.”

7) Clarifying that coverage does not include “administrative services” required to carry out studies but not required to furnish usual patient care.

8) Establishing a process that clinical research study sponsors/principal investigators must use to certify to CMS that their study meets the standards described in this policy.

9) Enumerating types of clinical research studies that are excluded from this policy.

10) Clarifying the relationship between coverage under this policy and local coverage determinations (LCDs).

The proposed NCD language is in the Appendix.

Finally, CMS is considering rulemaking to resolve some of the issues uncovered during this NCD reconsideration process. We hope to issue a Notice of Proposed Rulemaking on this subject shortly.

NCD Manual 310.1: Clinical Research Policy

Effective for items and services furnished on or after XXX XX, 2007, Medicare covers usual patient care in a clinical research study, under the circumstances described more fully below. The subject or purpose of the study must be the evaluation of an item or service that falls within a Medicare benefit category under Part A or Part B (e.g., physicians' service, durable medical equipment, diagnostic test) and is not statutorily excluded from coverage (e.g., cosmetic surgery, hearing aids). In addition, Medicare covers reasonable and necessary items and services used to prevent, diagnose, and treat complications arising from participation in these research studies.

Items and services furnished to Medicare beneficiaries in clinical research studies that do not meet the requirements of this policy are not covered.

1. Definitions.

Administrative services: Administrative services are defined as all non-clinical services, such as investigator and coordinator salaries; protocol development; recruiting participants; data quality assurance activities; statistical analyses; dissemination of findings; and study management. Administrative services also include clinical services provided to solely satisfy data collection and analysis needs that are not used in the direct clinical management of the patient.

Clinical research: Clinical research, for purposes of this NCD, means any systematic investigation involving human participants which is designed to contribute to generalizable knowledge and which involves a clinical intervention, care delivery strategy, or diagnostic technique designed to potentially improve predefined health outcomes.

Investigational clinical services: Investigational clinical services are defined as those items and services that are being investigated as an objective within the study. Investigational clinical services may include items or services that are approved, unapproved, or otherwise covered (or not covered) under Medicare.

National Coverage Determination Coverage with Evidence Development (CED) standards*:* Using the national coverage determination (NCD) process, the Centers for Medicare & Medicaid Services may determine, through an individualized assessment of benefits, risks, and research potential, that certain items and services for which there is some evidence of significant medical benefit, but for which there is insufficient evidence to support an evidence-based determination, are reasonable and necessary only when provided in clinical research that meets the requirements defined in that NCD.

Routine clinical services: Routine clinical services include items and services that:

- are covered for Medicare beneficiaries outside of a clinical research study;
- are used for the direct patient management within the study; and
- do not meet the definition of investigational clinical services.

For example, routine clinical services include:

- items or services required solely for the provision of the investigational clinical services (e.g., administration of a chemotherapeutic agent);
- clinically appropriate monitoring, whether or not required by the investigational clinical service (e.g., blood tests to measure tumor markers); and
- items or services required for the prevention, diagnosis, or treatment of research related adverse events (e.g., blood levels of various parameters to measure kidney function).

Usual Patient Care: Usual patient care includes routine clinical services and investigational clinical services in clinical research when the investigational clinical services would be covered outside of the clinical research and the clinical research meets the standards of a clinical research study defined in this policy.

2. Standards for clinical research to support Medicare coverage of items and services.

Medicare will cover items and services furnished through clinical research only when the following standards are met:

- The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
- The research study is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
- The research study does not unjustifiably duplicate existing studies.
- The research study design is appropriate to answer the research question being asked in the study.
- The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
- The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46. If a study is FDA-regulated, it also must be in compliance with 21 CFR Parts 50 and 56.
- All aspects of the research study are conducted according to the appropriate standards of scientific integrity.
- The research study has a written protocol that clearly addresses, or incorporates by reference, the Medicare standards.
- The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Studies of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life-threatening as defined in 21 CFR 312.81(a) and the patient has no other viable treatment options.
- The clinical research study is registered on the ClinicalTrials.gov website by the study sponsor/principal investigator prior to the enrollment of the first study subject.
- The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. However, a full report of the outcomes must be made public no later than three (3) years after the end of data collection.
- The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
- The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Exclusions from Required Standards: A number of data collection processes, while meeting the broad definition of a clinical research study, are based upon previously collected data, or data collected in such a manner as to not influence current patient management or health outcomes. The clinical items and services that are provided as the basis for these data collection processes may be determined to be reasonable and necessary under §1862(a)(1)(A).

These include:

- Simple non-comparative case reports and case series;
- Retrospective studies that evaluate events that have already occurred including studies that rely exclusively on previously collected administrative records, medical data or other available data;
- Quality assessment, quality improvement, or performance improvement studies; and

- Prospective studies in which natural human behavior is observed in a way that does not intentionally or unintentionally change or potentially change the behavior of patients, physicians and other clinical staff, control subjects, healthy volunteers, or caretakers; in which there is no assigned or pre-specified intervention that intentionally or unintentionally changes or potentially changes the behavior of patients, physicians and other clinical staff, control subjects, healthy volunteers, or caretakers; and in which there is no assigned or pre-specified intervention that changes or potentially changes medical care, medical decision-making or any medical treatments.

These studies are not required to meet the standards or approval processes outlined in this policy. All human subject protections and patient privacy rules continue to apply.

3. Coverage of Usual Patient Care and Coverage with Evidence Development.

Using processes outlined in this policy, Medicare covers usual patient care as defined in this policy. Medicare does not cover usual patient care when it is provided free to the Medicare beneficiary or when the study sponsor agreement with an investigator site or the informed consent documents provided to the patient specify that the clinical service will be provided free to all enrollees (§1862(a)(2); 42 CFR 411.4).

Through the national coverage determination (NCD) process, CMS may determine, through an individualized assessment of benefits, risks, and research potential, that certain items and services for which there is some evidence of significant medical benefit, but for which there is insufficient evidence to support an evidence-based determination, are reasonable and necessary only when provided in a clinical study that meets the requirements defined in that NCD.

4. Non-Coverage of Administrative Services.

Administrative services, as defined in this policy, in a clinical research study are not covered by Medicare.

5. Approval Process.

Effective XXXX, XX, 2007, CMS will cover usual patient care for beneficiaries enrolled in clinical research studies in which the study sponsor/principal investigator has certified to CMS that the standards as defined in this policy have been met. CMS will notify beneficiaries, providers, and practitioners of those research studies that have certified compliance with this policy by posting the research study title and ClinicalTrials.gov registry number on our website and in the Federal Register. The ClinicalTrials.gov registry will also annotate this in its registry. Providers and practitioners will add code modifiers and the ClinicalTrials.gov registry number to their claims forms indicating that usual patient care provided to beneficiaries in research studies occurred in research studies that were listed on the above sites as meeting the standards of the CRP.

Study sponsors/principal investigators wishing to have their research study listed as certified on our website, in the Federal Register and on ClinicalTrials.gov may send a letter to CMS describing the scope and nature of the clinical research, discussing each of the standards in this policy, and certifying that all standards in this policy have been met. CMS will only review this letter for completeness. Following approval of a Paperwork Reduction Act form, it will be provided on the CMS website to facilitate this submission. To be added to the list of certified studies, the letter should include the following information:

- Name of the research study
- ClinicalTrials.gov registry number ("NCT" followed by eight numbers)
- Study start date
- A point of contact with telephone number for questions if the letter is not complete.
- Discussion as to how the study meets each of the standards in this policy.

Letters should be submitted to:

Centers for Medicare & Medicaid Services
Office of Clinical Standards & Quality
Director, Coverage & Analysis Group
ATTN: Clinical Study Certification
Mailstop: C1-09-26
7500 Security Blvd
Baltimore, MD 21244

Clinical research studies required under CED will meet the approval process outlined in that NCD.

6. Exceptions.

Medicare will pay for covered services in clinical research studies where the study sponsor/principal investigator has certified that the study meets the standards as defined in this policy unless the CMS' Chief Medical Officer finds that the study does not meet the criteria outlined in this policy or the study jeopardizes the health or safety of Medicare beneficiaries.

7. Local Coverage Determinations.

Items and services provided within clinical research studies are subject to local policies including LCDs and claim adjudication. For information about LCDs, refer to http://www.cms.hhs.gov/DeterminationProcess/04_LCDs.asp#TopOfPage, a searchable database of Medicare contractors' local policies.

8. Investigational Device Exemption (IDE).

This policy is not applicable to, and does not change Medicare coverage according to the regulations on category A and categoryB investigational device exemptions (IDE) found in 42 CFR 405.201-405.215, 411.15, and 411.406.

9. Humanitarian Device Exemptions.

Since humanitarian use devices (HUDs) with an FDA approved humanitarian device exemption (HDE) are not addressed in this policy, local contractors may continue to make determinations about the coverage of HUDs.

10. Medicare Prescription Drug Benefit.

This policy is not applicable to and does not propose any changes to Medicare policies for coverage of prescription drugs under Medicare Part D.

11. Transition Plan.

This policy will not apply to any clinical research study that was covered under any previous policy that has begun enrollment prior to the effective date of this decision.

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[1] http://www.access.gpo.gov/nara/cfr/waisidx_05/42cfr52h_05.html

[2] http://www.cms.hhs.gov/mcd/ncpc_view_document.asp?id=8

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